

## Hyperactivation of B cells from Immunodeficient Patients

**Shawna K. McLetchie<sup>1</sup>**, Sarah N. Deffit<sup>1</sup>, and Gail J. Gardiner<sup>1</sup>

<sup>1</sup>Department of Microbiology and Immunology, IU School of Medicine

Chronic granulomatous disease (CGD) is an inherited immunodeficiency associated with defects in NADPH oxidase, an enzyme that produces oxygen radicals necessary to kill bacterial and fungal pathogens. NADPH oxidase, made up of six subunits, is located in endosomal and plasma membranes of immune cells. Although best studied in macrophages and neutrophils, the oxidase is expressed in B cells where we have shown its link to adaptive immunity and antigen presentation. Here, NADPH oxidase function was disrupted by mutations or gene knockdown in human B cells, and the role of the oxidase in innate immunity specifically Toll-like receptor (TLR) signaling tested. TLR7 and 9, which recognize viral single-stranded RNA and unmethylated CpG DNA respectively, potentially share an endosomal compartment with the oxidase in B cells. In this project, B cells were stimulated for 24 hours with TLR7 and 9 ligands along with a costimulator PMA. TLR7 signaling was significantly enhanced in oxidase deficient B cell lines compared with their respective control cells as evidenced by increased IL-6 secretion detected by an ELISA. CGD patients are incapable of producing oxygen radicals rendering them immunodeficient in terms of pathogen infection. Yet these patients also develop many autoimmune disorders associated with hyperactivation of the immune system. Thus, our studies on TLR activation using CGD cell lines may explain in part the development of autoimmunity in individuals with CGD. Additional studies are underway to examine the regulation of TLR including receptor expression levels and the subcellular localization of the NADPH oxidase in these B cells from CGD patients. This work has not yet been published and was supported by NIH 3R01AI079065-03S1.

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